UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,407	10/12/1999	TERRY L. DELOVITCH	087300-00040	5078

20350 7590 05/12/2003

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	25

DATE MAILED: 05/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/341,407	DELOVITCH, TERRY L.	
	Examin r	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/4/03 (Paper No. 23), is acknowledged.
Claims 2, 3 and 8 have been cancelled.
Claims 7 and 10-31 have been cancelled previously.
Claims 1, 4, 5 and 9 have been amended.
Claims *1, 4-6 and 9* are pending and are under consideration in the instant application.

2. In order to facilitate the prosecution of this application, Applicant is again requested to cancel all non-elected embodiments from the claims.

3. This Office Action will be in response to applicant's arguments, filed 3/4/03 (Paper No. 23). The rejections of record can be found in a previous Office Action (Paper Nos. 10, 15 and 21).

It is noted that New Grounds of Rejection are set forth herein.

Claim Rejections - 35 USC § 112 second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites "wherein the administered substance". However, claim 1, from which claim 4 depends, does not recite a "substance".

It is suggested that Applicant either amend claim 1 to insert -- a substance that is -- between "an effective amount of" and "an anti-CD28 costimulatory receptor..."; or limit claim 1 to the anti-CD28 agonist antibody and cancel claim 4.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Applicant's amendment, filed 3/4/03, has obviated the previous rejection of claims 1-6 and 8-9 under 35 U.S.C. 112, first paragraph, scope of enablement, by limiting claim 1 to the enabled embodiments acknowledged in Paper No. 21.

8. Applicant's amendment, filed 3/4/03, has obviated the previous rejection of claim 1 under 35 U.S.C. 112, first paragraph, *written description*.

Claim Rejections – 35 U.S.C. § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 4-6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over
Rabinovitch (Diabetes 43:613-621 1994, IDS-AH)
and Lenschow et al. (Immunity 5:285-293 Sept. 1996, IDS-Y),
in view of *either*
King et al. (Eur. J. Immunol. 25:587-595 1995, IDS-W), *or*
Webb et al. (Blood 86:3479-3486 1995, IDS-AQ).

Applicant's argument's, filed 3/4/03, have been fully considered with respect to the amended claims, but have not been found convincing, essentially for the reasons of record in Paper Nos. 10, 15 and 21.

Applicant's arguments are addressed below. The rejection of record may be found in Paper No. 10, and comments thereon in Paper Nos. 15 and 21.

The claims are drawn to a method of preventing the development of autoimmune diabetes in a susceptible subject by administering an anti-CD28 agonist monoclonal antibody.

As previously noted, Rabinovitch teaches that multiple immunostimulatory procedures prevent IDDM (autoimmune diabetes) in the NOD mouse (see entire document, e.g., "Title"). Rabinovitch also teaches that the immunostimulation protects from diabetes by favoring T cell differentiation along a protective TH2 pathway, thus downregulating the destructive TH1 response (e.g. page 616-619 "Immunostimulatory Procedures Prevent IDDM: Correction of a Cytokine Balance?", especially page 618-619 bridging paragraph). Rabinovitch concludes that the findings in the NOD mouse provide a basis for considering immunostimulation in attempts to prevent IDDM (autoimmune diabetes) in humans at risk for this disease (e.g., concluding paragraph page 619).

Applicant argues that administration of bacterial antigens, as taught by Rabinovitch, had been found not to function to delay onset of diabetes in humans prior to the filing date of the instant application. Applicant concludes that in view of these conflicting findings, one of ordinary skill in the art would not have had a reasonable expectation of success of upregulating the Th2 arm of the immune system.

However, it is noted that Applicant's comments and the comments in the unexecuted Declaration of Dr. Delovitch do not consider the teachings of Rabinovitch in the context of the combination of the references applied in the rejection of record, nor do they address the teachings of Rabinovitch regarding specific immune stimulation, as opposed to non-specific bacterial-mediated stimulation. Further, as noted previously and reiterated supra, Rabinovitch does teach that the immunostimulation protects from diabetes *by favoring T cell differentiation along a protective TH2 pathway* (e.g. page 616-619 "Immunostimulatory Procedures Prevent IDDM: Correction of a Cytokine Balance?", especially page 618-619 bridging paragraph).

As also previously noted, Lenschow et al. teach that the absence of signaling through CD28 in the NOD mouse leads to an accelerated development of diabetes due to the development of a dominant TH1 response (e.g., "Discussion" page 290, especially end of 1st full paragraph). Lenschow et al. further teach that the increased incidence of diabetes occurs when signaling through CD28 is blocked during the first two weeks of life (e.g., page 290, 2nd column, bottom ¼ of text).

Lenschow et al. conclude that it is a disruption of CD28 *signaling* from birth that exacerbates diabetes (e.g., page 289, last full sentence of 1st column). Lenschow et al. also note that disruption of CD28 signaling resulted in a decreased ability to mount a TH2 response (e.g., page 290 1st full paragraph). Throughout the Discussion on pages 290-291, Lenschow et al. clearly teach that it is the inhibition of CD28 signaling during the first two weeks of life that exacerbates disease, thus this teaching would suggest to one of ordinary skill in the art at the time the invention was made that the opposite method of stimulating CD28 signaling during this critical window would have the opposite effect of inducing a TH2 response and protecting from development of diabetes.

Applicant's comments regarding the complexities of the role of CD28 in the development of autoimmune diabetes in the NOD mouse are acknowledged.

Applicant further argues that the because there were other molecules that contributed to the development of GAD-specific (i.e., autoimmune) T cells in NOD mice lacking CD28, the complexities of the CD28 costimulatory pathway, and the fact that Lenschow et al. did not themselves comment on the application of CD28 agonists for prevention of diabetes in the NOD mouse, the ordinary artisan would not have had a reasonable expectation that the instantly recited method could be applied successfully.

However, as discussed supra and previously, the teachings of Lenschow et al., when considered in their entirety, address these confusing findings and conclude that the timing of the signal mediated by CD28 is critical (see entire document, but see especially comments at page 291, 1st column, concluding paragraph). That Lenschow et al. in the last paragraph of the Discussion on page 291 discuss antagonists of CD28 does not mean that the ordinary artisan at the time the invention was made would not readily appreciate that during the pre-diabetic stage, when blocking CD28 signaling exacerbates disease, an antibody that agonizes CD28 signaling would be desirable.

The Examiner maintains that even in view of the complex immune response studies by Lenschow et al., the ordinary artisan would take the teachings of Lenschow et al. for all they provide and conclude that since eliminating CD28 signaling from birth accelerates diabetes development, the opposite method of stimulating CD28 signaling during this critical window would have the opposite effect.

It is noted that Applicant again argues against the Rabinovitch reference and the Lenschow et al. reference individually; and the Examiner again points out that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As set forth in the original rejection in Paper No. 10, it is the combination of the teachings of the references and the inferences that the ordinary artisan would draw from them, taken together, that provides the basis for the instant rejection.

It is again acknowledged that neither Rabinovitch nor Lenschow et al. teach a method of preventing diabetes by administering an anti-CD28 agonist monoclonal antibody to a pre-diabetic subject identified as susceptible to developing diabetes

However, both King et al. and Webb et al. teach that a CD28 agonist monoclonal antibody induces a TH2 response (see entire document of each, especially "Abstract" and "Methods").

The Examiner maintains that, even in view of the complexities of the system as noted by Applicant, given the teachings of the references, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an agonistic anti-CD28 antibody in a method for preventing the development of autoimmune diabetes in a pre-diabetic subject susceptible to the development of diabetes.

The Examiner maintains that the ordinary artisan at the time the invention was made would have been motivated to administer an agonistic anti-CD28 antibody, such as those taught by King et al. or Webb et al., with the expectation of stimulating the development of a TH2 response, and thus preventing the development of diabetes in a pre-diabetic subject susceptible to developing diabetes, as taught by both Rabinovitch and Lenschow et al.

The Examiner maintains that the teachings of both King et al. and Webb et al. show that the ordinary artisan at the time the invention was made would have recognized that an antibody could be used to stimulate CD28, and further that this stimulation results in the TH2 type of response that both Rabinovitch and Lenschow et al. teach protects pre-diabetic susceptible subjects, including human subjects, from diabetes. Consequently, the ordinary artisan would have had a reasonable expectation of success in preventing development of diabetes in pre-diabetic subjects susceptible to the development of diabetes, including in humans.

The Examiner also maintains that in view of the teachings of Lenschow et al. that the critical window is in the first two weeks of life in the murine model, the ordinary artisan would have been further motivated to select pre-diabetic human subjects identified as susceptible to the development of diabetes for therapy in the corresponding period of life, i.e., at from about 6 months to about 2-3 years. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained as applied to the amended claims.

11. The Declaration of Dr. Delovitch under 37 CFR 1.132 filed 3/4/03 is insufficient to overcome the rejection of claims 1, 4-6 and 9 based upon the rejection under 35 USC 103(a) as being unpatentable over Rabinovitch and Lenschow et al. in view of either King et al. or Webb et al. as set forth in the last Office action because: the Declaration is unsigned.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

12. No claim is allowed.

13. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. This application contains claim 1which recites an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected inventions or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
May 5, 2003

Phillip Gambel
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
5/9/03